

### **REMARKS**

Upon entry of this amendment claims 1-4 are pending in the application. Claims 5-7 have been canceled.

#### ***Objection to the Specification***

In paragraph 2 of the office action the Examiner has objected to incorporation by reference to dbSNP. The specification has been amended to remove the incorporation by reference of the dbSNP entries corresponding to the SNP IDs listed in Table 1. The reference to the build and release date of the information has also been removed.

#### ***Rejection of Claims 1-4 Under 35 U.S.C. § 101:***

In paragraph 4 of the office action the Examiner has rejected claims 1-4 under 35 U.S.C. 101 as lacking utility. The Examiner asserts that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Applicants respectfully disagree.

The Examiner also asserts in paragraph 4 that the claims encompass SNPs in sequences that have not been taught or described by the specification. The Examiner reached this conclusion because (1) the specification teaches that for each of SEQ ID NO: 1-124,031 probes with a mismatch at any position in the sequence are contemplated and (2) the claims recited probes “consisting essentially of” one of the sequences. The Examiner indicates that because “consisting essentially of” is considered “open” because the specification does not define what is essential to the claimed nucleic acids that the claims would encompass SNPs other than those described by the specification. Applicants would like to clarify that the claimed probes do not include any unspecified variations in the sequences provided.

What Applicant is claiming in independent claim 1 from which claims 2-4 depend is an array of probes where each probe has a sequence that is identical to one of the sequences in the SEQ ID NO: 1-124,031 without variation or mismatch. The claimed probes already have the variation at the SNP position specified in the sequence. Applicants have used the “consisting essentially of” language to indicate that the probes may be attached to the array via a linker molecule or sequence, but the sequences provided in SEQ ID NO: 1-124,031 are the basic and novel characteristic of the claimed probes of the array.

The Examiner further asserts that the claimed array is not supported by a specific asserted utility because the specification provides no association between any of the SNPs interrogated by the array and a useful phenotype. Applicants respectfully disagree.

Section 101 of Title 35 of the United States Code states that for an invention to be patentable it must be useful:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Following the requirements of the Utility Examination Guidelines published at 66 FR 1092, Jan. 5, 2001, superseding the Revised Interim Utility Examination Guidelines that were published at 64 FR 71440, Dec. 21, 1999; 1231 O.G. 136 (2000); and correction at 65 FR 3425, Jan. 21, 2000; 1231 O.G. 67 (2000), a rejection based on lack of utility should not be imposed if the claimed invention has either a (1) well-established utility or the applicant has (2) asserted a specific and substantial utility that is credible. An assertion that the claimed invention is useful for a particular purpose is sufficient provided that the assertion would be considered credible by a person of ordinary skill in the art.

*The claimed invention has a substantial utility:*

In the utility guidelines training materials “substantial utility” is defined as “a utility that defined a ‘real world’ use”. Several uses for the collection of probes are disclosed in the specification. For example, on page 3, lines 8-14, of the specification the following uses for the arrays are disclosed:

monitor loss of heterozygosity; identify imprinted genes; genotype polymorphisms; determine allele frequencies in a population, characterize biallelic markers; produce genetic maps; detect linkage disequilibrium, determine allele frequencies, do association studies, analyze genetic variation, to identify markers linked to a phenotype or, compare genotypes between different individuals or populations.

Each of these asserted uses defines a substantial real world use for the claimed invention. The claimed invention is not a single probe or probes to a single SNP but probes to a collection of more than 10,000 carefully selected SNPs. Simply because the invention includes nucleic acid probes, the Examiner appears to require a demonstrated association between one of the SNPs and a “useful phenotype”. Applicants respectfully assert that this is a misapplication of the utility guidelines and a misunderstanding of the claimed invention.

Applicant is not claiming a single probe to a single SNP allele. What Applicant is claiming is an array of probes to interrogate simultaneously the genotype of a particular collection of more than 10,000 carefully selected SNPs that function together as a set of SNPs that represent the entire human genome. The SNPs were selected because they met specified criteria that allow them to function as a representative collection using the WGSa assay using the restriction enzyme XbaI. First, each SNP in the set is present on an XbaI fragment that is between 300 and 1000 base pairs. Second, the SNPs are selected so that they are spaced at an average distance of 210 Kb from one another so that no two SNPs would be expected to be tightly linked. Third, only SNPs that are polymorphic in multiple populations were selected so that the collection may be used for analysis of different populations.

In particular, the commercial embodiment of the claimed invention, the Affymetrix Mapping 10K array, has been used by researchers in linkage disequilibrium studies to identify disease related genes. In one study the Mapping 10K array was used to identify a mutation of *CNTNAP2* that is associated with cortical dysplasia-focal epilepsy (CDFE), a form of epilepsy found in Old Order Amish children. *See*, Strauss *et al*, *N Engl J Med*, 354:1370-7 (2006), a copy of which is provided herewith as Appendix A.

The researchers used the Mapping 10K array to genotype four affected children and their six parents. The genotype analysis identified a large block of autozygosity in the affected individuals. Of the 83 genes in the region, two candidate genes were selected for further analysis, *CENTG3* and *CNTNAP2*. A mutation in *CNTNAP2* was identified by sequencing and the four affected children were all homozygous for the mutation. All of the six parents were heterozygous for the mutation and an analysis of 105 healthy controls from the Old Order Amish population were analyzed and none were homozygous for the mutation. Seven additional individuals from affected families were identified as being homozygous for the mutation. Having identified a causative mutation, researchers and clinicians can screen individuals for the disease and begin treatment at a much earlier stage. This gene is now a candidate for analysis in children from other populations with forms of mental retardation, seizures and autism that have clinical symptoms similar to CDFE.

In addition to this one example study, Applicants have also provided a list of additional peer reviewed publications describing studies performed using the Mapping 10K array, see Appendix B. Applicants believe that the utilities asserted for the claimed invention are substantial and that this is demonstrated by the real world uses discussed above.

*The claimed invention has a specific utility:*

The training materials define a “specific utility” as “a utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class

of the invention.” A utility need not be unique to a claimed invention and can be shared by a class of inventions. Ex parte Fisher at 1028. The outcome of this analysis depends on what the broad class of the invention should be. Applicants assert that the broad class for comparison should be all possible collections of 124,031 twenty-five base nucleic acids probes. There are  $4^{25}$  different possible 25 base sequences so the number of possible combinations of 124,031 different 25 mers is very large. Clearly not all possible sets of probes would have the asserted utility of the presently claimed set of probes. These probes are all complementary to human SNPs and to a particular set of human SNPs. Other sets of probes could be selected that would be complementary to and capable of genotyping a collection of SNPs from humans, but there are estimated to be at least 5 million SNPs in the human genome so there would be many different combinations of 10,000 SNPs that could be selected. A set of probes to interrogate a different set of at least 10,000 human SNPs would not likely have the same utility as the claimed set of probes, because as indicated above this set of SNPs was selected to meet a specified set of criteria that allow them to function together in whole genome studies.

What Applicants are claiming is not an individual genomic sequence, but a collection of 124,301 genomic sequences that function as a set of probes to interrogate the genotype of a collection of more than 10,000 human SNPs. The SNPs were selected for inclusion in the set in order to obtain a set of SNPs that can be used for mapping the location of disease causing regions in the human genome. The probes interrogate the genotype of common polymorphic variants in the human genome. These SNPs are selected not because they are known to cause or to be associated with any particular phenotype or disorder, but because of their spacing throughout the genome and their ability to be assayed simultaneously using the Whole Genome Sampling Assay (WGSA). The WGSA includes a restriction digestion of genomic DNA with a selected enzyme (XbaI for these SNPs) followed by adaptor ligation of a common priming sequence to the fragments and PCR amplification. Only a subset of the fragments, those between about 300 and

1000 base pairs, amplify efficiently so the SNPs in the collection were selected to be on fragments in that size range when the human genome is digested with XbaI (see, specification at page 23, lines 3-9). Also, in order to maximize genome coverage, if two SNPs are close together only one was selected for inclusion.

The specification asserts a credible, substantial and specific utility for the claimed invention, making the rejection of the claims under 35 U.S.C. §101 improper.

***Rejection of Claims 1-4 Under 35 U.S.C. § 112:***

The rejection of the claims under the enablement provision of 35 U.S.C. §112 is a corollary of the finding of lack of utility and Applicants request that it be reversed for the same reasons set forth in Applicants' arguments above regarding the rejection under 35 U.S.C. § 101.

***Rejection of Claims 1-4 Under 35 U.S.C. § 103:***

In paragraph 10 of the office action the Examiner has rejected claims 1-3 as allegedly being unpatentable over dbSNP build 115 (June 1, 2003) in view of Venter (US Patent 6,812,339). Applicants respectfully disagree.

What applicant is claiming is a specific set of probes to genotype a specific set of probes to a specific set of more than 10,000 human SNPs that have been carefully selected from the more than 5 million known common SNPs. There is no teaching in dbSNP or Venter of the specific set of probes claimed or the specific set of SNPs targeted by the probes.

In paragraph 11 of the office action the Examiner has rejected claim 4 as allegedly being unpatentable over dbSNP build 115 (June 1, 2003) in view of Venter et al., (US Patent 6,812,339) and Lough et al., (US Patent 5,900,481). For the reasons discussed above the claimed invention is not obvious over dbSNP build 115 in view of Venter and Lough fails to remedy the deficiencies.

**CONCLUSION**

In view of the foregoing, this application should be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner has any questions pertaining to this application or feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5000.

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Respectfully submitted,

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